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PATENT SPECIFICATION

DRAWINGS ATTACHED

915.193



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COMPLETE SPECIFICATION

Process for the Manufacture of the Calcium and Ammonium Salts of Alpha-hydroxy-gamma-methylthiobutyric Acid

We, INVENTA A.G. FÜR FORSCHUNG UND PATENTVERWERTUNG, a Swiss Body Corporation organised under the laws of Switzerland, formerly of Haldenstrasse 23, Lucerne, Switzerland, now of Stampfenbachstrasse 38, Zurich 6, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to a process of simply and economically manufacturing the calcium salt of alpha-hydroxy-gamma-methylthiobutyric acid, and, more particularly, to an extraction process therefor. Also, the invention relates to a modified process for the manufacture and extraction of the ammonium salt of alpha-hydroxy-gamma-methylthiobutyric acid.

The calcium salt of alpha-hydroxy-gamma-methylthiobutyric acid also known as the calcium salt of the methionine hydroxy analog (MHA-Ca-salt), plays an important part in animal nutrition. Its action in the breeding and raising of fowl, according to the literature, compares with that of methionine. Even a slight admixture of this calcium salt to the feed effects not only accelerated growth of the animals, but also a better utilization of the feed. In a diet containing animal and vegetable proteins, the former can be replaced to a large extent by admixture of small amounts of MHA-Ca-salt.

The synthesis of the calcium salt of alpha-hydroxy-gamma-methylthiobutyric acid closely follows the production of methionine. For large-scale synthesis in production, the most suitable manner is by way of acrolein. Methylmercaptan is added onto acrolein in the customary manner, and the resultant methyl thiopropionaldehyde is reacted with hydro-

cyanic acid. By saponification of the methyl thiopropionaldehyde cyanohydrin, thus obtained, the alpha-hydroxy-gamma-methylthiobutyric acid is obtained. Saponification is carried out by means of a mineral acid, preferably sulphuric acid. After refining by customary methods, the excess sulphuric acid, after completion of the reaction is neutralized with calcium hydroxide or calcium carbonate. Large quantities of calcium sulphate are formed in this step which must be removed by filtration. If the precipitant is used in excess, the calcium salt forms which remains in solution in the mother liquor. The calcium salt can be recovered by evaporating the aqueous solution to dryness or at least to such a concentration that the product precipitates. Both processes have grave disadvantages for large-scale production. In the former case, very large amounts of calcium sulphate form so that the evaporation to dryness is rendered difficult in view of the evaporation temperature. Upon precipitating the calcium salt from the mother liquor, the precipitate carries much water with it so that difficulties ensue upon filtration. Moreover, an excess calcium carbonate or calcium hydroxide must be employed in order to assure complete reaction. Thereby, occlusions of the calcium salt in the calcium sulphate precipitated may occur which reduces the yield of the desired product. Generally, elevated temperatures are used at which with an excess of precipitant in alkaline medium, side reactions occur which again contribute to a reduction in yield. It has previously been suggested to carry the saponification in very concentrated acid to the amide step only and to precipitate therefrom, by dilution of the reaction solution, the alpha-hydroxy-gamma-methylthiobutyric acid amide. However, the isolation by this method does not occur quantitatively, so that the remainder of

the product must be recovered from the dilute mother liquor by an involved process.

It has also been suggested to extract the reaction solution after saponification with diethyl ether. After extraction, the solvent is evaporated, and the free alpha-hydroxy-gamma-methylthiobutyric acid is isolated. However, the high evaporation rate of the solvent precludes its use on a large scale. Other organic extraction agents hardly are usable.

We have now found a process, for the manufacture of the calcium salt of alpha-hydroxy-gamma-methylthiobutyric acid from an aqueous solution of the acid which comprises extracting the acid with an ether having a boiling point higher than ethyl ether, and adding to the extract calcium hydroxide or calcium carbonate in an amount equivalent to the acid. The extracting efficiency of the ethers used in the process according to the invention is not very high, so that a minimum of seven volumes of extractant for each volume of saponification solution must be used. The extracts obtained are of very low concentration so that, for the process to be economical on an industrial scale, the following preferred procedure is usually followed.

This preferred procedure is to saponify the methyl thiopropionaldehyde cyanohydrin in 10—25% sulphuric acid during 8—15 hours while refluxing. The alpha-hydroxy-gamma-methylthiobutyric acid in the reaction solution then is extracted to completion with an ether having a boiling point above ethyl ether, e.g., isopropyl ether, and separating the ether extract. 3—10 per cent by volume of water (calculated on the acid in the ether extract) are added to the ether extract, which contains 2—5 per cent alpha-hydroxy-gamma-methylthiobutyric acid, and the mixture is stirred with a rapidly moving stirrer in a stirring vessel so that a fine emulsion forms. The equivalent amount of the hydroxy acid of calcium carbonate or calcium hydroxide is added gradually in small portions. The calcium salt can also be suspended in water, at an amount necessary for such a suspension. With the addition of the calcium carbonate or hydroxide a very well crystallized precipitate of the calcium salt of alpha-hydroxy-gamma-methylthiobutyric acid forms. The termination of the reaction, which is attained after approximately 1—2 hours can easily be controlled by measuring the pH. The precipitate is then separated, for example, by means of a pressure filter. The water added to the ether is partly absorbed by the precipitate. The remainder separates in the filtrate from the ether. The latter is separated and can be re-used for a new extraction without first distilling or purifying it. The water remaining containing small quantities of the calcium salt, can be employed for the preparation of fresh

calcium carbonate or calcium hydroxide suspension, so that no losses occur in this portion of the process, either.

The mother liquor of the saponification, consisting of the sulphuric acid used and of the byproducts formed during the reaction, is treated at elevated temperatures with activated carbon. Practically all impurities are removed from the sulphuric acid by this process, so that the sulphuric acid can be used again.

The calcium salt of alpha-hydroxy-gamma-methylthiobutyric acid is removed from the pressure filter and is then dried. Since the extracting agents, i.e., the higher-boiling ethers, are selective for alpha-hydroxy-gamma-methylthiobutyric acid, a calcium salt of highest purity is obtained.

When calcium carbonate is used for the reaction, carbon dioxide forms which can be recovered and used for further synthesis. The preferred ethers are isopropyl ether and butyl ether, but equally good results are obtained with other higher-boiling ethers, e.g., n-propyl ether.

The technological advantages of the process according to the invention are obvious. The production can be carried out continuously which is of greatest importance for a large-scale industrial process. The calcium salt obtained is pure and contains no calcium sulphate, as is the case in processes relying on the precipitation of the sulphuric acid in the form of calcium sulphate. Moreover, the sulphuric acid used in the saponification is not lost as calcium sulphate, and only as much calcium carbonate or calcium hydroxide is employed as is required for the neutralization of the alpha-hydroxy acid. The ether used as extractant need not be distilled after use in the extraction, but can immediately be re-used without being subjected to any refining step. A great advantage in the employment of isopropyl ether resides in the fact that it extracts the calcium salt of alpha-hydroxy - gamma - methylthiobutyric acid extremely selectively. The same holds true for other higher-boiling ethers, e.g., n-propyl ether. The calcium salt precipitated is easily filtered and can be obtained in yields of more than 90 per cent.

The process also can be modified in such a manner that the alpha-hydroxy-gamma-methylthiobutyric acid is precipitated with ammonium from the extraction solution in the form of its ammonium salt instead of as the calcium salt. For this purpose, an amount of gaseous ammonia, equivalent to the acid present, is introduced into the extraction solution. Thereby, the salt separates as an oil and can be isolated by separation. If a slight excess ammonia is introduced, the extractant must be freed therefrom later on.

The following non-limitative example,

referring to the accompanying flow sheet, serves to further illustrate the invention:—

EXAMPLE

In the saponification vessel-1, filter to
 5 three quarters of the capacity and provided
 with a reflux condenser 2, 535 parts by weight
 20% sulphuric acid and 65 parts by weight
 methylthiopropionaldehyde cyanohydrin are
 kept boiling. The dwelling time is 10 hours,
 10 so that per hour 53.5 parts by weight sul-
 phuric acid and 6.55 parts by weight methyl-
 thiopropionaldehyde cyanohydrin are entered,
 and per hour, the equivalent amount of the
 reaction products are removed by way of con-
 15 denser 3 into the extraction column 4. The
 extraction is carried out by addition of 211.5
 parts by weight isopropyl ether by way of
 pipe 4a into the column 4. The extracted
 sulphuric acid whose amount corresponds to
 20 53.5 parts by weight is drawn off at the
 bottom of column 4 heated by means of heater
 11 to 90° C., conducted over the filter 12,
 containing activated carbon, and pumped back
 into the saponification vessel 1. The iso-
 25 propyl ether plus the extracted alpha-hydroxy-
 gamma-methylthiobutyric acid are removed
 from the top of column 4 and conducted into
 the precipitation vessel 5. The latter is filled
 to three quarters of its capacity and then
 30 contains 2313 parts by weight of the reaction
 product. Vessel 5 is provided with a very
 efficient stirrer and with a reflux condenser 6.
 Simultaneously, a suspension of 2.35 parts
 by weight calcium carbonate in 10 parts by
 35 weight water is removed per hour from stirrer
 vessel 7 and conducted into the vessel 5 by
 means of pump 8. Thereby, the hydroxy acid
 is reacted to form calcium salt of alpha-
 hydroxy-gamma-methylthiobutyric acid, which
 40 settles as a fine precipitate. The carbon
 dioxide formed in the reaction is removed
 through condenser 6. In order to maintain
 a balance of materials in the precipitation
 vessel 5, 229.5 parts by weight per hour of
 45 the reaction mixture are removed by way
 of the pressure filter 9a. The precipitated
 calcium salt is separated in filter 9a, whose
 dimensions are such that it can collect a pro-
 duction of 10 hours duration. As soon as the
 50 pressure filter 9a is filled, the reaction mix-
 ture is conducted to filter 9b. In this manner,
 77.7 parts by weight of the calcium salt of
 alpha-hydroxy-gamma-methylthiobutyric acid
 can be isolated within 10 hours, which con-
 55 tains 30 parts by weight water. The salt is
 dried in vacuo, and 92 per cent of the
 theoretical amount of the alpha-hydroxy-
 gamma-methylthiobutyric acid salt is obtained.

In settling vessel 10, calculated for a
 60 capacity of 1500 parts by volume, the filtrate
 is collected, whereby the ether and the

remainder of the added water separate. The
 isopropyl ether is removed in such a manner
 that per hour 211.5 parts by weight can be
 conducted into the extraction column 4. The
 separated water which still contains 0.5 parts
 by weight calcium salt, is recycled into the
 agitator vessel 7, wherein the required
 amount of 2.35 parts by weight calcium car-
 65 bonate and 3 parts by weight water per hour
 are added.

WHAT WE CLAIM IS:—

1. A process for the manufacture of the
 calcium salt of alpha-hydroxy-gamma-methyl-
 thiobutyric acid from an aqueous solution of
 the acid, which comprises extracting the acid
 with an ether having a boiling point higher
 than ethyl ether, and adding to the extract
 calcium hydroxide, or calcium carbonate, in
 an amount equivalent to the acid. 75 80

2. A process for the manufacture of the
 calcium salt of alpha-hydroxy-gamma-methyl-
 thiobutyric acid, which comprises saponifying
 methyl thiopropionaldehyde cyanohydrin with
 sulphuric acid of 10—25 per cent concentra-
 85 tion, completely extracting from the resulting
 reaction mixture the alpha-hydroxy-gamma-
 methylthiobutyric acid formed with an ether
 having a boiling point higher than ethyl ether,
 separating the ether extract from the aqueous
 solution, adding to the ether extract 3 to 10
 per cent of water, calculated on the acid in
 the extract, which is present at approximately
 2 to 5 per cent by weight, with rapid agita-
 95 tion to form an emulsion, adding to the mix-
 ture calcium hydroxide or calcium carbonate
 gradually in small portions, in an amount
 equivalent to the acid, filtering and drying
 the precipitate formed; separating the ether
 from the water and directly re-using the
 ether; conducting the aqueous solution
 remaining after the ether extraction over a
 filter containing activated carbon, and re-using
 the sulphuric acid thus recovered and puri-
 100 fied for saponification. 105

3. A process as claimed in Claim 1 or 2,
 in which the ether is isopropyl ether, n-propyl
 ether or butyl ether.

4. A modification of a process as claimed
 in any preceding claim in which the ammo-
 110 nium salt is separated by adding gaseous
 ammonia to the extract in an amount equiva-
 lent to the acid contained therein, instead of
 calcium carbonate or calcium hydroxide.

5. A process for the manufacture of the
 calcium salt of alpha-hydroxy-gamma-methyl-
 thiobutyric acid substantially as described
 herein with reference to the example. 115

6. The calcium salt of alpha-hydroxy-
 gamma-methylthiobutyric acid whenever pro-
 120 duced by a process as claimed in any of
 Claims 1, 2, 3 or 5.

7. The ammonium salt of alpha-hydroxy-gamma-methylthiobutyric acid whenever produced by a process as claimed in Claim 4.

For the Applicants:

GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52, Chancery Lane, London, W.C.2.

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ERRATA

SPECIFICATION No. 915,193

Page 1, line 42, for "wit" read "with"
Page 1, line 42, for "hydro-" read "hydro-"
Page 1, line 62, for "mormer" read
"former"
Page 2, line 86, for "synthesis" read "syn-
theses"
Page 2, line 120, for "ammonium" read
"ammonia"
Page 3, line 4, for "fillter" read "filled"
Page 3, line 5, for "the" read "its"

THE PATENT OFFICE
10th September 1964

